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Chronic Lymphocytic Leukemia, a Case Report

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ABSTRACT

Purpose of the presentation. The case presentation has as aim to describe the onset and evolution of a case of Chronic Lymphocytic Leukemia, (CLL), less common, which does not fit into the standard treatment criteria for malignant hemopathies.

Case description. The patient TA, female, 39 years of age, married, with 2 children, was admitted to the Emergency County Hospital of Targu Jiu in 2014, in the Internal Medicine Department for the Obstructive Chronic Bronchopathy with frequent coughing, night sweats, retrosternal pain. Clinical and ultrasound examination revealed splenomegaly, with spleen enlargement of 3 cm above normal diameters. The patient was also in the Endocrinology department with the diagnosis of Type II Diabetes and Grade III Obesity.

Laboratory results. Hemogram in 3 Diff revealed Hb = 14g / dL, Ht = 45%, Nr. Platelets of 275,000 / mm cub, but an increased number of Leucocytes, 117,000 / mm cub, and in the leucocyte formula from peripheral blood, the lymphocyte count was 80%, the absolute value being 9360. All biochemistry assays were in normal values, inclusive LDH = 375 md / dL, (N = 200-400 mg / d L. In the cytological examination of the peripheral blood smear stained with My Grunwald-Giemsa staining in the LPF 100 microscopy, was described the lymphocytosis with very small lymphocytes in high percent.

Conclusions; CLL onset occurs in a young female patient, contrary to the frequency of LLC in people over 65 years of age, especially in men. The normal baseline Hb, Ht%, Platelet counts in establishing the CLL diagnosis directly in stage I / II could be falsely positive due to the patient's comorbidities with COPD and DZ type II and Obesity. Also low platelet counts in the final stage III / IV may be appropriate for the LLC disease stage or may be low due to applied chemotherapy.

Keywords: Chronic lymphocytic leukemia, p-53 protein, monoclonal antibodies from the CD receptor panel, CD38 receptor.

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1. Introduction

Chronic lymphocytic leukemia,(CLL), is a heterogeneous disease, clinically characterized by the accumulation and expansion of a clone population of mature B lymphocytes in blood, bone marrow and lymphoid organs. Initial, genetic events are primarily responsible for the first stage of malignancy transformation and the processes of development and progression of CLL clone are considered to be modulated by signals of different micro-cellular environment, which regulates cell proliferation and survival of malignant B cells.

CLL is characterized by a progressive of antigen-stimulated mature B lymphocytes in blood, bone morrow and secondary lymphoid tissues. CLL is considered to be identical with small lymphocytic lymphoma (SLL), with different tissues manifestations. SLL is a term used when the malignant cells infiltrate solid tissue without overt leukemia in the blood.

CCL occurs in middle aged and elderly person, affecting men to women in approximately 2;1. Many patients are asymptomatic when the disease is diagnosed. Patients with minimal evidence of disease, ie, lymphocytosis only, are considered to be early stage of disease, while those demonstrating compromise of bone morrow function as anemia or thrombocytopenia, are in advanced stages.

Ray system has been modified to degree risk: stage „0", low risk, stage I and II intermediate risk and stage III and IV high risk. Stage '0'means lymphocytosis in blood and bone morrow only, stage I lymphocytosis plus enlarged lymph node, stage II lymphocytosis plus enlarged liver/and or spleen; lymphadenopaty may be present, stage III lymphocytosis plus anemia(hemoglobin< 11d/dl, lymph node, spleen or liver may be enlarged and stage IV with lymphocytosis and thrombocytopenia, PLT < 100 x10^3 /mm^3, anemia or organomelia may be present. Approximate, survival time in these 3 categories are greater in than 10, 6 and 2 years, respectively.

The Binet staging system is also effective in predicting prognosis, with median survival, ranging > 120 month in stage A, 61 month in stage B, and 32 months in stage C. Stage A means Hb > 10g/dl, PLT < 100 x $10^3/mm^3$,< 3 anatomic sites implicated; Stage B, Hb > 10g/dl, PLT > 100 x $10^3/mm^3$,> 3 anatomic sites implicated and stage C, Hb <10 g/dl, PLT < 100 x $10^3/mm^3$.Extreme lymphocytosis > 500 x$10^3/mm^3$ may occurs in late stage of the disease, hemolytic anemia occurs in case of complicated disease LLC with autoimmune hemolytic anemia , with reticulocytosis . The leukocyte count varues but most patients leucocytosis , 30 x $10^3m//^3$

The FAB group proposed 2 subtypes of LLC: subtype with small and large lynphocytes and subtype with increased pro-lymphocytes, approximately 10%-15%. In most case of CLL, lympfopcytes appears small with condensed chromatin pattern, and narrow rims of scant cytoplasm. The lymphocytes tend to resemble one another. Smudged or damaged lymphocytes often are prominent in the smear. (*Bennet JM, Daniel MT. Proposal for classification of cgronic (mature), Band T lymphoid leukemia, FAB. J. Clin Pathology. 1989: 42: 567-84).*

Prolymphocytes appear frequently present and are identified by their large size, lossely condensed chromatin, single nucleoli and small to moderate amount basophilic cytoplasm. The bone morrow in CLL, usually is hipercelular with variability increased number of lymphocytes with similar aspect as in peripheral blood. In the most forms of CLL, the cells are inert and arrested in G0/G1 of the cell cycle and there is only a small proliferative compartment; however, the progressive accumulation of malignant cells will ultimately lead to symptomatic diseases [1].

The diagnosis of CLL can be established initially by optical microscopy morphology combined with immune-phenotyping: monoclonal antibodies in the panel receptors CD5 +, CD

19+, CD20 + and CD23 +, CD28 wuth B lymphocytes which express IgM or IgD heavy chains or immune-glbulins with light chains kappa or lambda. Hypo-gama-globunlinemia occurs initially o during the course of the disease in most patients with LLC.

Intensely positive for CD20, FMC7 and / or CD79b, or coloring negative for CD23 immune-phenotyping, are seen as an atypical LLC. The receptor CD38+ is considered positive if population distinct lymphocytes exhibit a greater intensity of staining than granulocytes in the sample and is in association with proteins ζ model (ZAP-70). The protein ZAP-70 is a member of the protein-tyrosinekinase family. ZAP70 is normally expressed in T cells and natural killer cells, and has a critical role in the initiation of T-cell signaling. ZAP70 in B cells is used as a prognostic marker in identifying different forms of chronic lymphocytic leukemia (CLL), with a poor prognostic [2].

Various biological and genetic markers also have prognostic values. Clonal chromosomal abnormality by technique FISH can be detected until 80% from patients with LLC. The most clonal abnormalities involves long arm q of chromosome 13, and band 13q14, with relative good prognostic, trisomy 12, deletions 11q22-q23, 6q21-q23 and deletion 17p13, last associated with more advance disease or shortened survival times.

Patients with a del (17p) chromosome or P-53 gene mutation are refractory to repeated chemo-immuno-therapies [3]. In human body, the TP53 gene is located on the short arm of chromosome 17. The product of gene P53, protein p53 can arrests the growth cells by holding the cell cycle at the G1/S regulation point on DNA damage recognition. If the P-53 gene is damaged, tumor suppression is severely compromised. People who inherit only one functional copy of the P53 gene will most likely develop tumors in early adulthood, a disorder known as Li-Fraumeni syndrome [4]. P-53 gene may also be altered by mutagens (chemicals, radiation or viruses), increasing the likelihood of uncontrolled cell division. Through experimental research demonstrated that more than 50 percent of human tumors contain a mutation or deletion of P53 gene. Loss of function gene p53 creates genomic instability, which often leads to aneuploidy [5].

1.2. Case report

Patient, named TA, with 39 years of age, married, with 2 children, was admitted to the Emergency County Hospital of Targu-Jiu in 2014, in the Internal Medicine Department, with diagnosis of Obstructive Chronic Bronchopathy and symptoms as frequent coughing, night sweats, retrosternal pain. Clinical and ultrasound examination revealed splenomegaly, with spleen enlargement of 3 cm above normal diameters. The patient was also in evidence on endocrinology diagnosis with Type II Diabetes and Obesity (BMI = 55, calculated as [weight (kg)] / [height (m^2)], waist circumference = 96 cm, measured halfway between xiphoid and umbilical appendix, waist-hip ratio WHR)> 0.95, calculated as waist circumference / hips circumference (measured between the two trochanters).

1.3. Laboratory Examinations

Hemogram in 3 Diff revealed, Hb = 14g / dL, Ht = 45%, Nr. Platelets of 275,000 / mm cub, but an increased number of Leucocytes, 117,000 / mm cub, and in the leucocyte formula, the lymphocyte count was 80%, the absolute value being 9360. All biochemistry assays were in normal values, inclusive LDH = 375 md / dL, (N = 200-400 mg / dL).

The cytological examination of the peripheral blood smear stained with My Grunwald-Giemsa staining in the LPF 100 microscopy was described:

-Lymphocytosis with small lymphocytes with round nuclei, condensed chromate, insufficient cytoplasm and prolymphocytic on smear less than 1%. Morphological features were considered atypical for irregular or chromatin-dispersed nucleic acid lymphocytes, along with relatively frequent atypical Gumprecht nuclear

shadows, a microscopic picture characteristic of the diagnosis of Chronic Lymphocytic Leukemia, [Figure1]. Bone marrow aspirates revealed a 30% lymphocyte with a normal G / E ratio.

In order to specify the type of LLC, the patient chose to go to the University Hospital in Targu Mures where he continued the investigations in the Department of Clinical Hematology of the Hospital, where the Fllow Cytometry examination was revealed by immunophenotyping: monoclonal antibodies from the CD5 receptor panel CD2 +, CD22 +, CD22 +, bright CD23 +, bright CD28 +, CD28 +, for B lymphocytes. The strongly positive color for CD20, FMC7 and CD79b negative and intense staining for CD23 were seen as a typical immunophenotype in cell LLC type B. The CD38 receptor was a more negative prognostic sign.

1.4. Treatments

The treatment was initiated with mono-chemotherapy in CLL diagnosis, established at Stage I / II, continued until 2016, with Clorambucil (Leukeran®), which is the most commonly used and most tolerated cytotoxic drug. P.O. (associated with prednisone 40-60 mg) but the clinician did not reveal a remission of the disease. Then continued with chemotherapy associated with two cytostatic, (Leukeran plus Fludarabine (Fludara®) which is a nucleoside adenine analogue and is currently the most effective anti-LLC drug, continuing treatment until 2018.

In the last examination, at the end of the recommendation of the type of treatment, in the presentation of patients in the oncology department of the County Hospital of Targu Jiu, in the differential count was highlighted, RBC = 4.82 x 10 ^{3}x10^{3}µL, Hemoglobin 13.2 g / dL , Hematocrit 39.6%, erythrocyte count MCV = 82.1 fL, HCH = 27.4 µg, MCHC = 33.4 g / dL, RDW = 20.6, Platelet = 96 x 10^{3} µL. No. total leukocytes in HLG was 66.4 x 10^{3} µL and in the differentia count a percent of 75% lymphocyte count was found, along with a lymphocyte apoptosis lymphocyte morphology of 2%. The Hematologic Analyzer LH-750 signaled Flags: Leukocytosis, Anisocytosis, Thrombocytopenia.

The patient was harvested for Hemogram and Biochemistry to investigate the presence of the p-53 protein in peripheral blood lymphocytes which measured in high value of 4.30 U/ml (n=2.15). Following these investigations, the LLC diagnosis was established at the advanced stage III / IV and the patient, upon returning to the university clinic, was given treatment with the Tyrosine Bruton Kinase inhibitor, Ibrutinib, a more effective cytostatic agent in the event of deletion or mutation of the gene P-53.

2. DISCUSSIONS

2.1. P-53 isoforms and cancer

Recent research has shown that the P-53 gene is a tumor suppressor gene and its activity inhibit tumor formation. In the cell, the p53 nuclear protein binds to DNA by stimulating another gene, CDKN1A, to produce a protein called p21 that interacts with a cell-splicing protein (CDK2). In this context, it was shown that the nuclear protein p-53 protects the cell of a malignant process and the cytoplasmic protein p-53 through its isoforms can gain new functions to promote carcinogenesis. It has been shown that acetylation and deacetylation and phosphorylation of the p-53 protein are reversible processes and can repair DNA damage in cancer cells. The spectrum of cancer phenotypes due to mutations in the P-53 gene is also supported by the fact that different isoforms of the p53 protein have different cellular mechanisms in cancer.

Modified activity of the p-53 protein in isoform affects DNA damage and extends from the light to severe phenotype of cancer. [6].

These findings suggest that phosphorylation of the p-53 protein at Serin-15 amino acid is therefore an important focal point in p53 activation. Amino acid replacement, serine alanine caused partial failure of p53 to inhibit cell cycle progression.

TIGAR is a new p53 activating gene that inhibits glycolysis by reducing cellular levels of fructose

2,6-bisphosphate, a glycolysis activator and gluconeogenesis inhibitor. The active TIGAR site is open and positively charged, consistent with its enzymatic function such as bi-phosphatase. Also, the p53 protein has been identified as an important regulator of glucose transport and the transcriptional repression of both GLUT1 and GLUT4 receptors has been demonstrated. By contrast, the p-53 mutant does not affect GLUT1 and GLUT4 receptor activity in the malignant cell [7].

It has been shown that P-53 gene mutations are frequently detected in an allele of 17? -LL patients, occurring in more than 75% of cases. Patients with both abnormalities have a significantly weaker result than deleting a single 17p [8, 9] allele.

Another mechanism that can trigger P53 dysfunction is expression of MDM2 expression. Expression of MDM2 involves suppressing a large number of p53 and miRNA genes, including miR-34a, a downstream effect of p53. [10].

Frequent changes in the -P53 gene were found in more than 75% of LLC cases. Overexpression of MDM2 involves suppressing a large number of p-53 dependent genes and mRNAs, including microRNA-34a. Since this microRNA is involved in the induction of apoptosis depression and cell cycle disruption, a more aggressive course of the disease can be correlated with excessive expression of microRNA 34 [11].

CLL patients presenting deletion of the 17p chromosome were also associated with increased CD20, FMC7, CD79b receptor on B cell surface. In addition, an increase in CD38, ZAP-70 and IGHV expression in 17p [12, 13] deleted cases have been reported.

Prognostic patterns commonly used in CLL patients included clinical factors (mainly based on lymphocyte doubling time, Rai and Binet staging systems), molecular markers (CD38 expression, ZAP-70, IGHV mutational status), and abnormalities chromosome. With the new findings provided by NGS, the cytogenetic model has been proposed to integrate through the analysis of recurrent genetic mutations, as most of them have shown that they have an independent clinical impact on survival of patients.

Expression of unchanged immunoglobulin heavy chain variable (IGHV) genes, ZAP-70 and CD38 proteins, the appearance of chromosomal abnormalities such as 17p and 11q deletions and mutations of NOTCH1, SF3B1 and BIRC3 genes were associated with poor prognosis. In addition, mutations in tumor suppressor genes, such as TP53 and ATM, have been associated with resistance to conventional chemotherapeutic agents. Changes in micro-RNA expression and aberrant methylation patterns in genes that are specifically deregulated in CLL, including the BCL-2, TCL1 and ZAP-70 genes, have also been encountered and related to distinguished clinical parameters [14].

In addition, increased expression of CD38 receptors, ZAP-70 protein kinase and non-mutant IGHV chains has been reported in 17p deletions, resulting in poor prognosis of this group of patients ZAP70 in B cells is used as a prognostic marker in identifying different forms of chronic lymphocytic leukemia (CLL), with a poor the p53 protein: a prospective strategy for cancer therapy. prognosis.

2.2. Autophagy, a process mediated by p53 protein: a prospective strategy for cancer therapy.

Autophagy is a cellular process involved in the degradation of subcellular components that can be a source of proteins involved in tumorigenesis. Despite its role in maintaining genomic stability, numerous studies indicate a tumor supportive function that allows tumor cells to respond to stress stimuli such as nutrient deficiency and hypoxia, thus extending the life of the cell. Furthermore, tumors with autophagic deficits have been shown to be more susceptible to several chemotherapeutic agents [15].

In this case, autophagy promotes the survival of cancer cells and protects them from the action of drugs that induce apoptosis. Adjusting autophagy is quite complicated. This involves a series of signaling cascades, including p53. Recent reports have shown that p53 protamine plays dual roles in regulating autophagy depending on its sub-cellularity. Many cancer cells contain inactivating mutations of p53, which explains why cancer cells continue to live [16].

Under these conditions, the p53 protein has been shown to mediate genes that induce autophagy and stimulate autophagy by inhibiting mTOR complex, an AMPK-activated protein kinase (AMPK), [17]. Consistent with this role, p53 activity is compromised in a large proportion of all cancers, either by mutation of the P53 gene (p53 encoding) or by modifying p53 modulator status. The contextual role of autophagy in cancer, which could be changed by the p53 status, is expected to be developed into a new anticancer therapeutic approach.

3. The particularity of the case

LLC onset occurs in a young female patient, contrary to the frequency of LLC in people over 65 years of age, especially for men. The normal baseline Hb, Ht%, Platelet counts in establishing the LLC diagnosis directly in stage I / II could be falsely positive due to the patient's comorbidities with COPD and DZ type II and Obesity. Also, low platelet counts in the final stage III / IV may be appropriate for the LLC disease stage or may be low due to applied chemotherapy.

Also, hypoxia from COPD and hyperglycemia from DZ should be the factors that have activated the carcinogenesis pathways in LLC, increasing the Inducible Factor of Cellular Hypoxia, HIF, Myc oncogene activation, and signaling and activation pathways for tyrosine kinase phosphorylation, including and P-53 protein isoforms as transcription factors on malignant pathways. The patient remained in observer in both hospitals in which he presented himself.

4. Differential diagnosis of lymphocytosis from CLL

-Malignant Non-Hodgkin Lymphoma

- Hodgkin Lymphoma with the form rich in lymphocytes

- Multiple Myeloma

-Acute Lymphoblastic Leukemia

- Infectious Mononucleosis

-Viral Lymphocytosis

-Benign reactive Lymphocytosis (catarrh disease)

Of these, the hematologist is confronted more frequently with the following: cell lymphoma, follicular lymphoma, marginal splenic lymphoma, lympho-plasmocytic lymphoma, Hairy leukemia, prolymphocytic leukemia B. The history of the disease, the physical examination, and in particular the cytomorphologic examination of the peripheral blood, are useful, but they are only indicative. The cytological aspect may be suggestive for diagnosis Hairy cell leukemia, large granular lymphocytic leukemia and pro-inflammatory leukemia, or can only raise suspicion in case of low-grade non-Hodgkin's lymphoma. Differentiation is based only on the immunophenotypic aspect revealed by flow cytometry, the CD23 receptor abundance, the presence of CD25 receptor, CD103, CD79b.

Conclusion

P-53 gene mutation is the most common genetic abnormalities of cancer. They have been extensively studied in various malignancies of mature B cells, including CLL. In the latter, more attention has been paid to the importance of the p-53expressing protein in CLL and an association with poor survival and non-response to classical conventional chemistry therapy radiotherapy, in a number of CLL cases.

1.2.3.4.5. Patient education

-The observation of the respected recommended treatment schemes by the medical examiner at the university clinic,

-Reviewing the dietary status specified by a nutritionist

-Effectiveness of a slow, slow, non-aggressive weight loss treatment

-Exposure to toxic, macro-microclimate exposure.

-An active and rational life regime as a prophylactic factor for the progression of carcinogenesis.

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